Economic Evaluation of Ibrutinib as First-Line Treatment of Unfit Patients with Chronic Lymphocytic Leukemia in the Netherlands and the Potential Role of Precision Medicine

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Research report
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Summary

Chronic lymphocytic leukemia (CLL) is the most common form of leukemia in adults in Western countries. The prognosis for younger patients with CLL can be relatively good but the life expectancy of older (>65 years) or unfit patients is significantly impaired. Less than 60% of these older patients are alive 5 years after the diagnosis.

The current standard treatment in the Netherlands for this type of cancer is obinutuzumab combined with chlorambucil (GClb). However, about a quarter of the patients do not respond to this treatment. A new therapy with ibrutinib shows promising results compared to GClb but it comes at very high costs. Currently ibrutinib is not reimbursed in the Netherlands for these patients. This study evaluated the cost-effectiveness of ibrutinib compared to GClb in the treatment of unfit CLL patients in the Netherlands, from the societal perspective. It also studied the potential of a possible test that can predict which patients are expected not to respond to GClb and how it affects the cost-effectiveness of treating only these patients with ibrutinib.

A partitioned survival model was developed with three mutually exclusive health states: progression-free survival (receiving or not receiving therapy), progression, and death. Curves for progression-free survival and overall survival were extrapolated based on the results of two randomized controlled trials. Utilities were derived from an elicitation study on CLL health states in the UK. Costs and background mortality were obtained from a variety of Dutch sources.

Ibrutinib was estimated to lead to 1.79 more life-years (LYs) and 1.17 more quality-adjusted life years (QALYs) compared to GClb, at an additional cost of €432,224. This combined led to €240,913 costs per LY gained and €369,657 (95% C.I.: €190,169-1,160,357) per QALY gained.

The effect of a possible stratification test that predicts the treatment response to GClb on the ICER was modeled. The percentage of patients with a complete response to GClb (22.3%) was combined with the median time of no progression for these patients (76 months). The stratification test leads to 1.12 more QALYs and €320,421 in additional costs compared to GClb. This combined leads to an ICER of €285,847 (C.I.: €149,051-434,968) per QALY gained compared to GClb.

Ibrutinib for previously untreated and unfit CLL patients in the Netherlands is not a cost-effective strategy compared to the standard treatment of GClb when an €80,000 ICER threshold is used. A possible test predicting the individual response to GClb can lower the incremental costs while having a similar gain in QALYs. But even this strategy of using a stratification test is estimated not to be cost-effective compared to standard treatment.
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Introduction

Chronic lymphocytic leukemia (CLL) is the most common form of leukemia in adults in Western countries (SEER, 2017). In this type of blood cancer the white blood cells are affected. The disease is mainly diagnosed in the elderly and predominantly in men. Diagnosing CLL is relatively clear-cut, but the exceptional clinical heterogeneity complicates the treatment decision a physician needs to make (Baliakas et al., 2016). A lot of patients are diagnosed at an early stage of the disease and a so called ‘watch-and-wait strategy’ is recommended (Chen et al., 2017). However, the majority of the patients require treatment eventually (Chen et al., 2017). While treating younger people with CLL can be quite successful, older (>65 years) and unfit patients have a worse prognosis. Less than 60% of these patients are alive after 5 years (NCIN, 2015).

Unfit CLL patients in the Netherlands currently receive the standard treatment of chlorambucil plus an antibody (HOVON, 2016). There are several combinations with chlorambucil available but the most effective is the combination of obinutuzumab plus chlorambucil (GClb). However, about a quarter of the patients do not respond to this standard treatment with GClb (Goede et al., 2014). These patients on average experience progression of their cancer within 12 months from the start of the treatment and the overall survival they face is significantly impaired (Santacruz et al., 2014).

A new drug called ibrutinib targets the leukemia cells directly and it has shown big potential in overcoming these limitations of GClb. While there is no direct comparison available between ibrutinib and GClb, clinical trials suggest that ibrutinib has a better overall response rate and a longer estimated survival than GClb (Burger et al., 2015). The problem is that ibrutinib treatment leads to very high costs. Drug expenses for ibrutinib are approximately $130,000 per patient per year and these expenses need to be made until patients progress or have significant toxicities (Chen et al., 2017).

While current standard treatment with GClb is not always effective, the newer and more effective treatment with ibrutinib is costly. Although studies show that ibrutinib can increase the life expectancy of these patients, at this moment it is not reimbursed in the Netherlands. So it would be meaningful to know if ibrutinib can offer value for money. What is the cost-effectiveness of ibrutinib and should it be reimbursed? An economic evaluation of ibrutinib in the first line has not been performed before but it is important to know. The Dutch healthcare budget is already under pressure and reimbursing ibrutinib can add millions of additional expenses to this tight budget (Zorginstituut Nederland, 2017).

It might turn out that it is not a cost-effective strategy to treat all patients with ibrutinib. But what if you only treat the fraction of the patients that are not expected to respond to GClb with
ibrutinib and treat the other patients with GCib? Is it cost-effective to stratify patients with CLL according to their response to GCib? For this kind of predictive stratification, a test is needed that can identify which patients will respond to GCib. This treatment strategy is called precision medicine. First of all, this can be beneficial for the patients due to increased life expectancy. Secondly, it is also promising from an economic perspective (Annemans, Redekop, & Payne, 2013). The high costs of ibrutinib will only be made for patients not responding to the cheaper treatment of GCib. So even when ibrutinib turns out to be cost-effective, the test can still be valuable since it can possibly lower treatment costs while retaining the medical benefits.

This predictive test is currently hypothetical and is not yet developed. But before development takes place, it would be of interest for designers of this test to know if such a test can be cost-effective at all when used for stratification of untreated CLL patients. In addition, it would be valuable to know what the minimum sensitivity and specificity for this test needs to be in order to be cost-effective. The answers to these questions can serve as a target for the designers for the minimum performance of a hypothetical test to be cost-effective. This test could in the end save money and – more importantly – save lives in the treatment of CLL. So the question answered in this study is: What is the cost-effectiveness of ibrutinib as first-line treatment of unfit patients with chronic lymphocytic leukemia in the Netherlands and can a predictive test make ibrutinib (more) cost-effective?

The study starts with the Theoretical framework which contains an outline of the current state of knowledge regarding clinical aspects of CLL in general, the clinical and cost aspects of ibrutinib and GCib, and information on (early) cost-effectiveness analyses. This is followed by an extensive section on the Research methods used. The Results are presented afterwards and this research report is ended with a Discussion and conclusion.

**Theoretical framework**

**CLL in general**

As mentioned before, CLL is a type of blood cancer in which the formation of white blood cells is disturbed. Too much white blood cells are produced and crowding out of normal cells takes place (American Cancer Society, n.d.). This increases the risk of serious infections and it can lead to excess bleeding, bruising and to shortage of red blood cells (Cancer Research UK, n.d.). It distinguishes itself from the acute type of leukemia because the abnormal white blood cells can mature partly but not completely. Another characteristic is that it starts in the cells that become lymphocytes.
The majority of CLL patients are diagnosed at a later stage in life. More than 70% of the new CLL-cases in the Netherlands get the diagnosis of CLL at an age over 65 years (Nederlandse Kankerregistratie, 2017). CLL seems to affect males more than females: in 2015 there were 797 new cases of CLL in the Netherlands, 497 (62.4%) were male and 300 (37.6%) were female.

Not every patient diagnosed with CLL needs treatment immediately (Jain & O’Brien, 2015). When symptoms are mild or absent, a physician can choose for a ‘watch-and-wait’ strategy and monitor the disease regularly (Chen et al., 2017). One of the monitored factors is whether or not the disease progresses. Assessing the progression of CLL is based on these factors formulated by the international CLL group (Hallek et al., 2008). The occurrence of at least one of the following:

- The emergence of new lesions (>1.5 cm) or an increase in the size of existing lesions by at least 50%, or
- hepatomegaly (enlarged liver) or splenomegaly (enlarged spleen), or an increase of 50% of a previously noted increase of these organs, or
- increase in the number of lymphocytes in the blood by at least 50%, or
- decrease in the number of red blood cells, white blood cells or platelets (cytopenia) attributable to CLL, or
- transition to an aggressive histological image.

When the disease progresses there are multiple treatments available ranging from chemotherapy, treatment with antibodies and targeted therapies among others.

**Treating unfit CLL patients**

The treatment of CLL is determined by the health state of an individual patient. This study focused on unfit patients. These patients have serious comorbidities (WHO classification 3-4) and cannot receive chemotherapy (HOVON, 2016). As noted earlier, the current standard first-line treatment of unfit CLL patients in the Netherlands is chlorambucil plus an antibody called monoclonal anti CD20 (HOVON, 2016). Chlorambucil can be combined with several different antibodies. The Dutch guideline advises the combination of obinutuzumab plus chlorambucil (GCib) to obtain the longest progression-free period. Obinutuzumab is given by infusion into a vein (IV) and this can take up to several hours. Chlorambucil comes in the form of a tablet. GCib has a median progression-free survival (PFS) of 29.9 months; see Figure 1 (Goede et al., 2015). However, not all patients respond to GCib; in fact, 22.3% of the patients do not respond to it and 55.0% only show a partial response (Goede et al., 2014).
Over the last couple of years, oral targeted agents like ibrutinib, have showed their potential in clinical trials (Chen et al., 2017). Ibrutinib (brand name: Imbruvica) has a 30-month PFS rate of 96% which is considerably better than 30-month PFS rate of 50% with GCib (Coutré et al., 2017). Figure 2 shows the results of ibrutinib compared to chlorambucil regarding PFS. Next to the improved clinical outcome, ibrutinib is also well tolerated, even in extended treatment. Ibrutinib is not given intravenous, like obinutuzumab, but is taken in pill form. It is a prime candidate for first-line therapy for unfit CLL patients: ibrutinib as first-line therapy has a high overall response rate (ORR) of 86% (Burger et al., 2015).
In Figure 3 the results of the clinical trials with GC1b and ibrutinib are combined to make the treatments easier to compare. It does not only show the PFS from Figure 1 and 2, but also the difference in overall survival.

![Graph showing PFS and OS of GC1b and ibrutinib](image)

**Figure 3.** Progression-free survival and overall survival of GC1b and ibrutinib (Burger et al., 2015; Goede et al., 2015)

**Ibrutinib too expensive?**

Ibrutinib shows promising results in clinical trials but it comes with very high costs. Ibrutinib costs approximately $130,000 per year and it is advised to continue treatment until patients progress or have significant toxicities (Chen et al., 2017). Currently, ibrutinib is not reimbursed in the Netherlands as first-line treatment (Cats, 2016). Reimbursement is put on hold and ibrutinib is placed in a so-called ‘pakketsluis’ by the Dutch Minister of Health (Schippers, 2016). In the meantime the National Health Care Institute will work on an advice and the proper usage regarding reimbursement. This advice can be used by the Minister of Health in negotiations with the drug manufacturer on the price. While ibrutinib is in the ‘pakketsluis’ patients do not have insured access to the drug. The manufacturer has the option to make ibrutinib available to patients with urgent medical needs. However, the pharmaceutical company behind ibrutinib made clear that they have no intentions to do this.
New and costly treatments like ibrutinib could strain the Dutch healthcare budget. The current system in the Netherlands is already struggling with the access to cancer medicine and it can insufficiently guarantee access in the near future (KWF Kankerbestrijding, 2015). It is argued that pharmaceutical companies ask unreasonable high prices that are not proportionate to the development costs. The Dutch National Health Care Institute advised to consider (hard) criteria for the reimbursement of medicines (National Health Care Institute, 2015).

In this light it is important to know to what extent patients could benefit from ibrutinib relative to the costs that are made. Only then it is possible to assess if it is worth it, or if you can get more value for your money by investing it in other treatment/programs in the healthcare sector. This assessment is called a cost-effectiveness analysis. One form of this analysis is a cost-utility analysis (CUA). The important aspect of a CUA is that it uses a generic measure of health gain (Drummond, Sculpher, Claxton, Stoddart, & Torrance, 2015). This measure is usually expressed as quality-adjusted life years (QALYs).

A cost-utility analysis of ibrutinib compared to GC1b has not been performed for first-line therapy in the Dutch healthcare setting. This analysis has been performed for relapsed patients and ibrutinib is shown to be cost-effective for these patients (Welten, Ignacio, & Verheggen, 2016). Also in other countries there is no economic evaluation performed comparing ibrutinib to GC1b. NICE was not able to formulate a recommendation about ibrutinib in the first line because it did not receive evidence submission from the manufacturer Janssen-Cilag (NICE, 2017b).

There is no explicit ICER threshold in the Netherlands that determines whether a treatment is reimbursed or not. The National Health Care Institute, instead, advised on using reference values (Zorginstituut Nederland, 2015). These reference ICERs – referred to as ‘soft’ threshold – are dependent on the specific disease burden. The combinations of disease burden and maximum incremental cost (€) per QALY are as followed:

<table>
<thead>
<tr>
<th>Disease Burden</th>
<th>Maximum Incremental Cost (€) per QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1 till 0.4</td>
<td>€20,000 per QALY</td>
</tr>
<tr>
<td>0.41 till 0.7</td>
<td>€50,000 per QALY</td>
</tr>
<tr>
<td>0.71 till 1.0</td>
<td>€80,000 per QALY</td>
</tr>
</tbody>
</table>

**Partitioned Survival Model**

To analyze the cost-utility of the two different treatments a Markov model can be used. This model is “based on a series of ‘states’ that a patient can occupy at a given point in time” (Drummond et al., 2015, p. 331-332). The Markov Cohort Model (MCM) is based on explicit transition probabilities to change from one state to another in every discrete time period. The length of this time period, the cycle, should be chosen so the probability of two or more ‘events’ within one cycle is minimized.
Other important inputs in the model next to the transition probabilities are costs and the utility of being in a certain state. An approach similar to the Markov Cohort Model is also used regularly in economic analyses within health care: the Partitioned Survival Model (PSM). This is also called the area under the curve (AUC) model. The PSM is similar to the MCM in its use of mutually exclusive health states. However, the distribution of the cohort is not based on explicit transition probabilities but on the area under the curve of the Kaplan-Meier functions (Minacori, Bonastre, Lueza, Marguet, & Levy, 2015). The number of patients in the progressed state is determined by subtracting the proportion of people that are alive and free of progression (PFS) from the proportion of patients alive (OS). An example can be found in Figure 4. PSM has the advantage of being transparent and less assumptions are necessary. It is seldom described in theory but regularly used by NICE to assess cost-effectiveness (Minacori et al., 2015). Comparing two different treatments with a Markov model will lead to an incremental cost or saving per quality-adjusted life-year gained.

\[
S(t_{1})_{\text{progression}} = S(t_{1})_{\text{OS}} - S(t_{1})_{\text{PFS}}
\]

![Figure 4. Calculation of the proportion of patients in progressed state (Minacori et al., 2015)](image)

Precision medicine in CLL

The cost-effectiveness of ibrutinib as first-line treatment for all unfit patients is one aspect worth studying. Treating patients with ibrutinib instead of GCib seems promising because only a quarter of the patients receiving the standard treatment with GCib show complete response. Clinical outcome can thus be improved by treating everyone with ibrutinib as shown above. But it also means that a quarter of the patients will receive the expensive ibrutinib treatment while the cheaper GCib would have sufficed. This leads to another interesting aspect to study: what if you could stratify patients beforehand based on their expected response to GCib? Patients that are expected not to respond to this treatment can get ibrutinib as first-line treatment.
Predicting how individual patients respond to a certain treatment is an emerging field within medicine. It is often referred to as ‘precision medicine’ which is defined as: “treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations” (Jameson & Longo, 2015, p. 2229). The heterogenous clinical manifestation of CLL and interpersonal differences with respect to response to treatment makes CLL an interesting candidate for precision medicine.

While the use of predictive characteristics is rather new in treating CLL, prognostic characteristics have been used for decades (American Cancer Society, n.d.). Prognostic indicators are used to stratify patients according to their estimated clinical outcome. This prognostic stratification does not take the individual treatment response into account but these indicators might also be useful to do just that. Baliakas (2016) elaborates on the current prognostic indices/scores in CLL. All of these indices/scores have their shortcomings. Currently none of them are universally accepted and adopted in clinic. The authors state that while a universal prognostic model is beyond reach in the short term, a focused effort on patient subgroups and specific decision points, like first-line treatment, “may provide a more accurate approach”. Stratification based on the responsiveness of GC1b is a prime candidate of such an accurate approach.

As mentioned before, predictive indicators could possibly be based on prognostic indicators, but it is important to know the distinction. A prognostic factor is defined as “a situation, condition or characteristic of a patient that can be used to estimate outcome due to the disease irrespective of the treatment given” (Zenz, 2010, p. 72). The previously mentioned article of Baliakas (2016) summarizes these factors. A predictive marker is a condition that predicts efficacy of a particular therapy based on marker status (Zenz, 2010). These kind of markers are also called pharmacogenomics (study of several genes) and pharmacogenetics (study of single genes) (Berm et al., 2016). The many prognostic factors relating to CLL that are currently identified could possibly be used as a predictive factor. For most of these factors the predictive power regarding response to different treatments must still be determined. However, research in CLL is shifting rapidly from prognostic markers to predictive markers.

**Early cost-effectiveness analysis**

Precision medicine is not only beneficial for the patient, healthcare payers can also benefit from this stratification. The high costs of ibrutinib will only be made for patients not responding to the cheaper treatment of GC1b. However, before development of a stratification test takes place, it would be of interest for designers of this test to know if the use of a test can be cost-effective strategy at all. In
addition, it would be valuable to know for developers what the minimum sensitivity and specificity for this test needs to be in order to be cost-effective.

These kind of analyses that estimate the cost-effectiveness of tests or treatments before getting to the market are called ‘early cost-effectiveness analyses’ (Buisman et al., 2016). This is in contrast with ‘late cost-effectiveness analyses’ which are economic evaluations of treatments or tests already on the market, like the CEA of ibrutinib.

The value of information

The focus so far has been on the uncertainty surrounding individual heterogeneity in the response to the standard CLL treatment. It is also possible to focus on the uncertainty surrounding treatment outcome in general. This is a different line of reasoning within the scope of health technology assessment (HTA) and one of the concepts of interest is the concept of value of information (VOI). This notion stems from the fact that a lot of decisions in healthcare are made with uncertainty on the effectiveness and costs of a certain treatment (Bindels et al., 2016). VOI is a tool that researchers or decision makers can use to explore this uncertainty and to estimate the value of additional data collection. It can be used to determine an optimal research design to obtain this additional information. The research design is influenced by the combination of the probability of an incorrect decision and its monetary consequences. The value of perfect information (EVPI) can be calculated.

The value of information also plays a role in real options analysis (ROA). This kind of analysis can support the decision problem of reimbursing a current treatment or wait till more evidence is collected (Grutters et al., 2011). The trade-off is between the risk of a suboptimal therapy versus the risk of not reimbursing an optimal therapy. The choice depends for a large part on how costly it is to reverse a decision (Eckermann & Willan, 2008). If the decision is irreversible or very high costs need to be made to reverse the decision it is preferred to delay the decision and collect more information. For decisions that are reversible at relative low costs it is preferred to adopt the technology while collecting more information.

Although there is considerable uncertainty surrounding the clinical effects of ibrutinib compared to GClb due to a relative short follow-up period, that is not the primary issue studied here. The first issue of the early CEA is whether a stratification test can be cost-effective at all. In this analysis there is no explicit role for VOI. This role, however, will become meaningful if a test in theory can be cost-effective. In that case the value of the information from the test related to the sensitivity, specificity and the consequences from incorrect stratification will be of great importance.
Research methods

The Cost Utility Analysis (CUA) of this study consists of two main parts. Part I is a CUA of ibrutinib compared to GClb as first-line treatment of unfit CLL patients in the Dutch healthcare setting. This part will compare arm 1 and arm 2 of the decision tree (Figure 5). The analysis in part II will largely be based on the CUA comparing ibrutinib and GClb but it will extend the analysis and will focus on the potential role of the stratification test. Only patients that are predicted not to show complete response to GClb will receive ibrutinib. According to the clinical trial this will be 22.3% of all CLL patients. So part II will compare arm 1 and 3 (Figure 5). It will determine how the cost-effectiveness of ibrutinib changes when the stratification test is used.

Figure 5. Decision tree

P: unfit CLL patients in the Netherlands without previous therapy
I: intervention I: ibrutinib for all patients; intervention II: the use of a hypothetical stratification test that can predict which patients will show complete response to GClb
C: GClb
O: costs (€), life-years (LYs) and quality-adjusted life-years (QALYs)

As mentioned before, statements about the cost-effectiveness of a treatment or a test are usually based on models combining the clinical effects and the economic costs. Part I describes in detail the general model used in this analysis and its different variables. A number of consecutive steps have been taken, including: choosing a model structure, extrapolate survival-functions from the literature, assigning utility values to different health states, and including all relevant costs. In addition to the base case result, a sensitivity analysis is performed to take the uncertainty in the different parameters into account. The model was generated using Microsoft Excel. Part II describes how this
general model from part I is extended to analyze the potential role of precision medicine in treating CLL.

Research methods part I – CUA of ibrutinib vs. GCib

In part I the option of treating all patients with GCib (Figure 5 – arm 1) is compared with the option of treating all patients with ibrutinib (Figure 5 – arm 2). Both of these options are modelled using a Markov model with three main health states: progression-free survival, progression of disease and death (Figure 6). It is common in modelling studies of CLL to use these three states (Casado et al., 2016). The state of progression-free survival (PFS) has two substates: patients can either be receiving therapy or not. A specific utility value and cost was assigned to each health state.

![Figure 6. Markov Model with three health states.](image)

All patients start in the progression-free state (PFS) and after each model cycle a patient can stay in a particular state or move to one of the other states. Transitions can only occur according to the arrows in Figure 6, so death is an absorbing state.

The treatment cycle of GCib is 4 weeks. In order to prevent that two events can occur within one model cycle, a shorter model cycle length was chosen. Transitions were assumed to happen every 2 weeks; this means that each treatment cycle of GCib consists of two cycles of the model. Ibrutinib has no treatment cycle but is given every day till progression. The model cycle length for ibrutinib is similar as for GCib because of practical reasons.
Fitting of the survival curves

The trials that study ibrutinib (Burger et al., 2015) and GClb (Goede et al., 2015) do not compare the drugs directly. Next to that, the follow-up period for ibrutinib was only 24 months. So first it was checked whether there were other relevant randomized clinical trials (RCTs) with a direct comparison or longer follow-up periods. The most recent systematic literature review on interventions for unfit patients with chronic lymphocytic leukemia was performed by Städler et al. (2016). Furthermore, Chen et al. (2017) included trials in its economic burden analysis of CLL that represented the best available evidence at that time. A hand-search on PubMed, Google Scholar, Clinicaltrials.gov (US National Institute of Health), Evidence.nhs.uk (UK National Health Service) and Dclls.org (German CLL study group) was done to complement the clinical trials of interest from these two studies. Unfortunately, there were no other relevant RCTs in additional to Goede et al. (2015) and Burger et al. (2015).

Since there was no trial performed that directly compared ibrutinib with GClb, an indirect comparison was made. The study populations of Goede et al. (2015) and Burger et al. (2015) have similar base characteristics (Table 1), so comparing their efficacy was assumed to be legitimate. The study on ibrutinib contains no Dutch patients but a diverse population with many European patients is studied. There is only one Dutch patient in the study on GClb but also this study contains a diverse set of patients with a lot of patients from Germany.

<table>
<thead>
<tr>
<th></th>
<th>Obinutuzumab-chlorambucil</th>
<th>Ibrutinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>N. of patients</td>
<td>333</td>
<td>136</td>
</tr>
<tr>
<td>Median age</td>
<td>74</td>
<td>73</td>
</tr>
<tr>
<td>Range in age</td>
<td>39-89</td>
<td>65-89</td>
</tr>
<tr>
<td>Male sex</td>
<td>61%</td>
<td>65%</td>
</tr>
<tr>
<td>Unmutated IGHV</td>
<td>62%</td>
<td>43%</td>
</tr>
<tr>
<td>Del(17p)</td>
<td>7%</td>
<td>0%*</td>
</tr>
<tr>
<td>Del(11q)</td>
<td>16%</td>
<td>21%</td>
</tr>
<tr>
<td>Source</td>
<td>Goede et al. (2014)</td>
<td>Burger et al. (2015)</td>
</tr>
</tbody>
</table>

Table 1. Demographic and clinical characteristics of patients in RCTs – * ineligible for study

The Partitioned Survival Model (PSM) was used to assess the distribution of the cohort over the different health states. For the extrapolation after the trial follow-up period the assumption is that the treatment of ibrutinib gives continuous benefit after the trial period. According to Drummond et al. (2015, p. 318), this is a reasonable assumption in the case the treatment is continued after the end of the trial follow-up.

First, the Kaplan-Meier curves of the clinical trials have been imported using Engauge Digitizer. The method of Hoyle and Henley (Hoyle & Henley, 2017) was used to fit different distribution in RStudio. This method can provide estimates of the survival time that are almost as
accurate as estimations based on actual IPD (Wan, Peng, & Li, 2015). Extrapolation was estimated using multiple parametric distributions: Exponential, Weibull, Lognormal, Log-logistic and Generalized Gamma. The best fit for each Kaplan-Meier curve was primarily selected based on the Akaike information criterion (AIC) of each distribution. A lower AIC value is an objective indication of a better fit (Ishak, Kreif, Benedict, & Muszbek, 2013). The best fit according to the AIC was then checked on the basis of visual inspection and knowledge of the clinical manifestation of CLL. The data on AIC and Bayesian information criterion (BIC) of the distributions can be found Appendix A. The different fitted distributions are shown in Figure 7, 8, 9 and 10.

The Kaplan-Meier curve for the OS of GClb shows a sharp decline after 30 months, which is not in line with the trend before 30 months (Figure 9). At this point in time there were not a lot of patients at risk in the RCT so this gives quite some uncertainty regarding the fitted distributions. As can be seen in Figure 9 these fitted distributions do not seem to take this decline into account. The main concern is that these fitted distributions show an overall survival curve that is too optimistic. Since these distributions can have a large impact on the results and median OS is not reached for the GClb arm, the distributions were checked using the hazard ratio of the other arm of the study. In Appendix B the KM-curve of Clb (blue) and GClb (red) can be found. Information on the AIC and BIC of these distributions can be found in Appendix C. The hazard ratio from Goede et al. (2015) of 0.41 was used to get the distributions showed in this graph. Comparing the distribution with the best fit (Exponential) with the corresponding curve from GClb in Figure 9 it seems like the curves are quite similar. The fitted curve from Clb even showed a better median OS than the fitted curve from GClb (162 months vs 144 months). So there is no indication based on the fitted curve from Clb that the main concern was true. This fitted curve from Clb gives an even more optimistic survival curve than the fitted curve from GClb. So it was decided to use the fitted curve of the GClb since it is the most direct way of fitting the distribution.

Data from Statistics Netherlands (2017c) is used to estimate the background mortality unrelated to CLL. The area under the PFS-curve and OS-curve is supplemented with this background mortality. The reason why this is done is because extrapolation is based on the KM-curves of RCTs with relative short follow-up periods. The mortality rate during this follow-up is probably dominated by CLL-related death. But when extrapolating over a longer period of time, at some point the mortality rate unrelated to CLL can be higher than the CLL-related mortality rate. Supplementing the survival curves with background mortality is done by taking the maximum of the probability of death based on the fitted curve and the probability of death in the Netherlands based on age and sex.

Half-cycle correction is used to determine the number of patients in a health state during a certain time period.
Figure 7. Progression-free survival with GClb (Goede et al., 2015)

Figure 8. Progression-free survival with ibrutinib (Burger et al., 2015)
Figure 9. Overall survival with GC1b (Goede et al., 2015)

Figure 10. Overall survival with ibrutinib (Burger et al., 2015)
Population

The cohort of patients with CLL that was simulated with this Markov model was based on the sample of patients studied by Burger et al. (2015) and Goede et al. (2015). The starting age of the simulated cohort is 73 years old, in line with the median age of these clinical trials. Since the dosage of chlorambucil is based on the body surface area (HOVON, 2016), the mean body weight (73.5kg) and mean height (168.6cm) of persons aged 75 year or older in the Netherlands (Statistics Netherlands, 2017b) were used to estimate the dosage used. This was based on the body surface area calculated according to the Mosteller formula.\(^1\)

As mentioned earlier, the distribution of CLL in the Netherlands between men and women is similar as in the RCTs used (see Table 1). It is unknown if the age of the studied patient population is in line with the age of treated CLL patients in the Netherlands.

Utilities

Utilities for the different health states of CLL are derived from a utility elicitation study performed on 100 members of the UK general public (Kosmas et al., 2015). This elicitation study used the EQ-5D questionnaire. This is a standardized instrument to measure generic health states (EuroQol Group, 2017). The members of the general public rate possible health states of CLL along five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For the study by Kosmas (2015) the EQ-5D was used with 3 levels on every dimension: no problems, some problems, and extreme problems (EQ-5D-3L). The Dutch guideline (Zorginstituut Nederland, 2016) prefers using the EQ-5D questionnaire with 5 levels (EQ-5D-5L): no problems, slight problems, moderate problems, severe problems, and extreme problems. In addition, the guideline prefers using Dutch valuation of the different health states. However, there is no EQ-5D-5L with Dutch valuation available for CLL so the EQ-5D-3L from Kosmas (2015) will be used without country adaptation.

Kosmas (2015) reports TTO utility and VAS scores for nine different states regarding CLL. TTO will be used in the analysis because it is a choice-based method and, unlike scaling, this is a natural human task (Drummond et al., 2015, p. 135). In the sensitivity analysis the 95% C.I. of the TTO method is used. The utility values can be found in Table 2.

---

\(^1\) Mosteller formula: body surface (m\(^2\))=[[height (cm) * body weight (kg)/3600] \(\frac{1}{2}\).
### Table 2 Parameters of the model

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Base case value</th>
<th>Sensitivity analysis (range)</th>
<th>Distr. for PSA S.E.</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristics of the patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>73</td>
<td></td>
<td></td>
<td>Goede et al. (2014), Burger et al. (2015)</td>
</tr>
<tr>
<td>Body weight</td>
<td>73.5</td>
<td></td>
<td></td>
<td>CBS (2015)</td>
</tr>
<tr>
<td>Height</td>
<td>168.6</td>
<td></td>
<td></td>
<td>CBS (2015)</td>
</tr>
<tr>
<td>Body surface area</td>
<td>1.86</td>
<td></td>
<td></td>
<td>Calculated (a)</td>
</tr>
<tr>
<td><strong>Distribution for PFS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weibull</td>
<td>Exponential, Lognormal, Log-logistic, Gen. Gamma</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Distribution for OS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exponential</td>
<td>Weibull, Lognormal, Log-logistic, Gen. Gamma</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Health state utilities</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFS without therapy</td>
<td>0.82</td>
<td>0.78-0.85*</td>
<td>β 0.017*</td>
<td>Kosmas (2015)</td>
</tr>
<tr>
<td>PFS on initial therapy oral treatment</td>
<td>0.71</td>
<td>0.67-0.75*</td>
<td>β 0.02*</td>
<td>Kosmas (2015)</td>
</tr>
<tr>
<td>PFS on initial therapy IV treatment</td>
<td>0.67</td>
<td>0.63-0.71*</td>
<td>β 0.022*</td>
<td>Kosmas (2015)</td>
</tr>
<tr>
<td>Progression after first line treatment</td>
<td>0.66</td>
<td>0.62-0.71*</td>
<td>β 0.022*</td>
<td>Kosmas (2015)</td>
</tr>
<tr>
<td><strong>Drug costs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Obinutuzumab (1000mg)</td>
<td>€ 3,960.26</td>
<td>€ 3168.20-€4752.31**</td>
<td></td>
<td>Zorginstituut Nederland (2017)</td>
</tr>
<tr>
<td>Chlorambucil (per tablet 2mg)</td>
<td>€ 2.08</td>
<td>€ 1.66-€2.50**</td>
<td></td>
<td>Zorginstituut Nederland (2017)</td>
</tr>
<tr>
<td>Ibrutinib (per capsule 140mg)</td>
<td>€ 67.61</td>
<td>€ 54.08-€81.13**</td>
<td></td>
<td>Zorginstituut Nederland (2017)</td>
</tr>
<tr>
<td><strong>Cost of IV administration</strong></td>
<td>€ 198.73</td>
<td>158.98-238.48**</td>
<td>γ 39.75**</td>
<td>Gautney et al. (2013)</td>
</tr>
<tr>
<td><strong>Cost of adverse events</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>€ 1,858.77</td>
<td>1487.02-2230.53**</td>
<td>γ 471.08*</td>
<td>Bouwmans et al. (2009)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>€ 1,785.00</td>
<td>1428-2142**</td>
<td>γ 382.24**</td>
<td>Opendisdata (2012) - 990016113</td>
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<td>Hypertension</td>
<td>€ 2,189.58</td>
<td>1751.67-2627.50**</td>
<td>γ 437.92**</td>
<td>Opendisdata (2012) - 090301005</td>
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<tr>
<td>Infection</td>
<td>€ 2,660.00</td>
<td>2128-3192**</td>
<td>γ 532.59**</td>
<td>Opendisdata (2016) - 019999004</td>
</tr>
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<td>Infusion-related reaction</td>
<td>€ 940.00</td>
<td>752-1128**</td>
<td>γ 187.56**</td>
<td>Opendisdata (2016) - 182199008</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>€ 1,788.00</td>
<td>1430.4-2145.60**</td>
<td>γ 357.60**</td>
<td>Blommestein et al. (2016)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>€ 1,299.00</td>
<td>1039.2-1558.80**</td>
<td>γ 521.48**</td>
<td>Bouwmans et al. (2009)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>€ 1,593.00</td>
<td>1274-1911.60**</td>
<td>γ 318.60**</td>
<td>Blommestein et al. (2016)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>€ 3,493.19</td>
<td>2794.55-4191.82**</td>
<td>γ 434.53**</td>
<td>Bouwmans et al. (2009)</td>
</tr>
<tr>
<td><strong>Supportive care costs per cycle</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFS</td>
<td>€ 146.36</td>
<td>117.08-175.63**</td>
<td>γ 29.27**</td>
<td>Holtzer-Goor et al. (2014)</td>
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<td>Progression costs per cycle</td>
<td>€ 856.23</td>
<td>684.98-1027.48**</td>
<td>γ 171.25**</td>
<td>Holtzer-Goor et al. (2014), Blommestein et al. (2016)</td>
</tr>
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<td><strong>Discount rate</strong></td>
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<tr>
<td>Costs (year)</td>
<td>4%</td>
<td>0%</td>
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<td>Hakkaart-van Roijen et al. (2016)</td>
</tr>
<tr>
<td>Effects (year)</td>
<td>1.5%</td>
<td>0%</td>
<td></td>
<td>Hakkaart-van Roijen et al. (2016)</td>
</tr>
</tbody>
</table>

(a) Based on the Mosteller formula: body surface (m²) = [height (cm) * body weight (kg)/3600] ½.

* Based on corresponding literature ** 20% (+/-) of base case value

### Perspective

A societal perspective was taken, in accordance with the Dutch guidelines (Hakkaart-van Roijen et al., 2016). This means that not only direct medical costs are included but also indirect medical costs and productivity costs.
Costs

Direct medical costs

The Dutch guideline (HOVON, 2016) contains treatment schedules with the dosage and number of cycles for the two treatments. This can be found in Appendix D. All different costs are shown in Table 2.

The prices used in this model for obinutuzumab and chlorambucil are the reported reimbursement prices (Zorginstituut Nederland, 2017). These prices are comparable to other European studies on the cost-effectiveness of GClb (Blommestein et al., 2016; Casado, 2016). The assumption is that there is no drug wastage of obinutuzumab. This is common in cost-effectiveness studies on obinutuzumab (Blommestein et al., 2016; Casado, 2016). In practice this means that obinutuzumab given at day 1 (100mg) and day 2 (900mg) of the treatment (see Appendix D), is given from the same vial (of 1000mg). In the sensitivity analysis no vial sharing is assumed. This means that both on day 1 and on day 2 a new vial is used and the remainder of the vial on day 1 is thrown away.

Ibrutinib is currently reimbursed for certain conditions in the Netherlands but not yet for CLL in the first line (Nederlandse Zorgautoriteit, 2016; Medicijnkosten, 2017). But the estimated price of ibrutinib is assumed to be the same as the current reimbursement price of ibrutinib for these other conditions (Zorginstituut Nederland, 2017). This estimated price in the Netherlands is about five times as high as the current average wholesale price in the United States, where ibrutinib is already indicated for first-line treatment of unfit patients (Chen et al., 2017). In Italy the price of ibrutinib is similar as in the Netherlands (Aiello, D’Ausilio, Randon, & Lo Muto, 2016). Ibrutinib is made available in the United Kingdom for second-line treatment in November 2016 (NICE, 2016) but not yet for treatment naïve patients. The price, however, is confidentially negotiated by the National Health Service (NHS). The option of negotiating a lower price will be taken into account in the scenario analysis.

The total costs for these drugs can be lower than estimated if the actual cumulative dose differs from the planned cumulative dose according to the Dutch guidelines. For ibrutinib no information on the actual (cumulative) dose was found. For GClb only the actual median cumulative dose was provided. The actual median cumulative dose of obinutuzumab in Goede (2014) was 8000mg which is exactly according to the Dutch guideline. The actual median cumulative dose of chlorambucil was 396mg which is lower than would be expected according to the Dutch guideline (519mg). In the sensitivity analysis it is studied if this lower actual cumulative dose of chlorambucil, resulting in lower total costs for chlorambucil has an effect on the ICER.

Treatment administration cost of obinutuzumab was estimated at €199 (Gaultney et al., 2013). This amount was in line with studies of Blommestein et al. (2016) and Chen et al. (2017) that reported €184 (Euros 2012) and $220.62 (Dollars 2015) respectively.
Only adverse events of grade 3 or higher are included in the model and events with an incidence of 3% or more (Appendix E). This is common in cost-effectiveness analyses of CLL treatments (Blommestein et al., 2016; Casado et al., 2016). It is assumed for the calculations that all adverse events occurred during the first cycle. This is because all grade 3-4 infusion-related adverse events with GCib happened during the first infusion (Goede et al., 2014). Besides that, adverse events can be treated and kept under control by the physician so serious side effects at a later point in time are thus less likely to happen. Next to this, it is also common to apply the total costs of the adverse events in the first cycle as a one-time event (NICE, 2015; Becker et al., 2016). The costs of different side effects (Table 2) are based on multiple studies focusing on the Netherlands (Bouwmans, Janssen, & Uyl-de Groot, 2009; Blommestein et al., 2016; Holtzer-Goor et al., 2014) complemented with data of the Dutch Healthcare Authority (2017).

Supportive care costs are based on a Dutch study on real-world costs of CLL in the Netherlands (Holtzer-Goor et al., 2014). The costs of supportive care during PFS were based on the percentage of monthly costs of Clb treatment that was spent on monitoring (58.3%). According to Blommestein (2016), this is the best representation of the total monthly costs of patients treated with GCib. The treatment/supportive care costs of the progressed disease (PD) state were based on real-life costs (Holtzer-Goor et al., 2014) and real-life utilization (Blommestein et al., 2016) of patients in the Netherlands in the second line. Since the patients of interest are unfit and are not eligible for chemotherapy, all combinations with fludarabine (F, FC and FCR) are excluded in this estimate. The derivation of the treatment/supportive care cost of the PD state can be found in Appendix F.

**Indirect costs**

Treatments that increase the life expectancy of individuals can indirectly lead to more medical costs. During the life years gained, diseases unrelated to CLL can lead to costs. When using a societal perspective, these costs also need to be included in the model. Indirect medical costs are estimated with a Dutch costing tool (Van Baal et al., 2011). This tool provides age- and sex-specific per capita health expenditure per disease and stratified by time to death. Zweifel, Felder, & Meiers (1999) showed that healthcare expenditure depends on the time to death. The costing tool of Van Baal et al. (2011) contains the average age- and sex-specific expenditures of the last year of life and of other years. It is preferred to use these expenditures (Van Baal et al., 2011). However, this leads to too much modeling complexity since the model cycle is just two weeks and not a full year, which would be compatible with the costing tool in an easier way. This is the reason why the costs of living an additional year is used instead of the costs for deceased individuals and survivors for each age. The costs of living an additional year can be more easily be adapted to the model cycle of two weeks.
Indirect costs also include productivity losses so it is important to know how CLL affects the productivity of the patients. According to the Dutch cancer registration, more than 70% of the new CLL-cases in the Netherlands were diagnosed at an age over 65 years (Nederlandse Kankerregistratie, 2017). This means that a majority of people diagnosed with CLL are already with retirement. After diagnosis it can take years before treatment is necessary. Patients that are diagnosed before the legal retirement age can usually just continue to work as long as they do not need treatment (Arbeidsparticipatietool, n.d.). The majority of CEAs on CLL did not include productivity losses due to a healthcare perspective. Some that did include them (Hornberger et al., 2012) did that because median age of their study population was 61 years. The median age of the RCTs used in this CEA is 73 so the starting age of our model cohort is well after the legal retirement age in the Netherlands. Since all patients in the model already retired, we assume the productivity costs to be negligible.

Since a societal perspective is used, the travel time, time for receiving treatment and time for caregivers need to be included. To estimate these costs several parameters were based on the Dutch Guideline for Costs in Economic Evaluations (Hakkaart-van Roijen, van der Linden, Bouwmans, Kanters, & Tan, 2016). Other were assumptions made by the author. See Appendix G for all parameters. It is assumed that patients need to be monitored every 3 months after finishing their treatment with GCib and during their treatment with ibrutinib. This is in line with the Dutch guideline (HOVON, 2016).

The cost year of the study is 2017. Costs found in the literature are corrected for inflation using the Dutch CPI (Statistics Netherlands, 2017a). Half-cycle correction is used to determine the cost of ibrutinib treatment. This is not done for the treatment of GCib, since this treatment is given on the first day of a model cycle. The costs for GCib is made for all patients at the start of the model cycle while costs for ibrutinib are only made for patients in the progression-free state for each day of the model cycle.

**Time horizon**

A lifetime time horizon was used, in accordance with the Dutch guidelines (Hakkaart-van Roijen et al., 2016).

**Discounting**

According to the Dutch guideline (Hakkaart-van Roijen et al., 2016) costs need to be discounted at 4% and effects at 1.5%. A discount rate of 0% for both costs and effects was used in the sensitivity analysis.
Sensitivity analysis

A sensitivity analysis is performed to explore the effect of variability in the input values on the cost-effectiveness. First a univariate sensitivity analysis is performed. The upper and lower bounds used for this analysis can be found in Table 2. They are either based on information from the corresponding article or calculated as 20% lower and higher than the base case. This percentage is rather arbitrary but it is common in economic evaluations regarding CLL to use either 20% (Casado et al., 2016) or 25% (Blommestein et al., 2016). The results from the one-way sensitivity analysis are also presented in a tornado diagram (Drummond et al., 2015).

After the univariate sensitivity analysis, a probabilistic sensitivity analysis (PSA) was performed. This is recommended in the Dutch guideline (Hakkaart-van Roijen et al., 2016). A distribution that reflects the available evidence of that variable was assigned to each of the input variables. The distributions were then sampled using Monte Carlo simulations, and for every sample of inputs a single estimate of resulting costs and effects was calculated. This process was repeated 10,000 times. A gamma distribution was used for the resource use and a beta distribution for the utilities, in line with theoretical literature (Drummond et al., 2015) and with previous CEAs with respect to CLL (Hornberger et al., 2012). In the univariate sensitivity analysis the effect of using a different parametric distribution was analyzed. In the PSA, however, the variability of the distribution with the best fit was incorporated. This is because the parameters that determine the shape of the fitted PFS- and OS-curves can also be affected by variability. To internalize this variability in the shape, a Cholesky matrix is generated by RStudio for the different distributions. This matrix captures the variance and covariance of the distribution parameters. Using this matrix and the deterministic distribution parameters it is possible to incorporate the variability of the distributions in the probabilistic sensitivity analysis. The prices for the different drugs are kept constant in the PSA since there is no uncertainty regarding these prices because they are fixed at this moment based on agreements with the reimbursement authority. The combinations of incremental QALYs and costs resulting from the simulations were put in an cost-effectiveness (CE) plane.

In order to determine the probability that the treatment is cost-effective at a certain ICER threshold, the net monetary benefit (NMB) at each ICER threshold was calculated first (Drummond et al., 2015, p. 300). For every simulation it was determined whether ibrutinib or GClb had a higher NMB. The ICER threshold was varied between €0 and €800,000 and for every threshold the probability of the treatment to be cost-effective was calculated. This information was put in a cost-effectiveness acceptability curve (CEAC).

The relationship between the unit cost of ibrutinib and its cost-effectiveness is studied in the scenario analysis.
Research methods part II – early CUA of stratification test

Part II extended the model described in part I. It analyzed the cost-effectiveness of using a stratification test to determine which patients do not respond to GClb. The option of treating all patients with GClb (Figure 5 – arm 1) is compared with the option of using a predictive test (Figure 5 – arm 3). The same costs, utilities, PFS- and OS-curves, and other values are used as in part I. The difference is that one cohort of 1000 patients is modelled receiving the standard therapy GClb. This cohort is compared with a cohort of 1000 patients from which 22.3% receives GClb and the other 77.7% receives ibrutinib. This is based on Goede et al. (2014) in which 22.3% of the patients treated with GClb showed complete response.

A significant fraction of these patients have achieved a minimal residual disease (MRD) negative status (Santacruz et al., 2014). This means that the CLL is not detectable anymore in their blood or bone marrow even with the very sensitive current methods. The MRD negative status after complete remission can be seen as a prognostic indicator since trials have shown that these patients have a significantly longer survival than patients with residual disease (Bosch et al., 2008). The median treatment-free survival duration for patients with MRD negative status is 76 months (Santacruz et al., 2014). For the stratification test it is assumed that patients obtaining complete remission with GClb will stay progression-free for 76 months. During the first 76 months, this cohort only faces the Dutch background mortality.

It is assumed that all patients need second-line treatment after these 76 months. According to the Dutch guideline (HOVON, 2016), an unfit patient with late relapse (>36 months after first treatment) should be treated with chlorambucil plus a monoclonal anti CD20. However, available anti CD20 medication like obinutuzumab, ofatumumab and rituximab are not registered in the Netherlands for relapsed patients (HOVON, 2016). This means chlorambucil monotherapy is the only registered option. Fortunately, this is in line with second-line treatment in the RCTs used in the analysis. Patients receiving ibrutinib in the first line received chlorambucil in second line (ClinicalTrials.gov, 2017). Furthermore, most of the patients in the Netherlands receive chlorambucil after progression (Appendix F). Additionally, chlorambucil was the second most prevalent treatment in the progression state after treatment with GClb (Goede et al., 2014).

However, it seems that there has never been a RCT that has assessed chlorambucil in second line for unfit CLL patients. So to estimate the PFS and OS for these patients in the second-line, a study on chlorambucil in the first line is used instead (Eichhorst et al., 2009). Patients receiving first-line treatment in general have a better prognosis than patients receiving a similar treatment in the second line (Fischer et al., 2011, 2012). This means that the effect of chlorambucil on PFS and OS in the second line should be worse than when the estimation is based on the effect of first-line
treatment. But this is countered by the assumption that these patients showed a complete response to a chlorambucil treatment in the first-line. This makes a better response in the second line more likely (Rossi, 2007). The Kaplan-Meier curves for the PFS and OS can be found in Appendix H. The corresponding table with information on the fit can be found in Appendix I.

For the base case analysis the test was assumed to have a 100% sensitivity and specificity as well as to have price of €0. Based on the initial results, different combinations of sensitivity and specificity were intended to be tested for cost-effectiveness at different ICER thresholds. The price was also intended to be varied to find out at what price and with what combinations of sensitivity/specificity the use of the test along with ibrutinib treatment could be cost-effective.

A sensitivity analysis was performed to explore the effect of the variability in the parameter values on the results. This was done in a similar way as in part I.

**Results**

**Results part I – CUA of ibrutinib vs. GCib**

**Base-case analysis**

The results from the base case scenario show the improvement in clinical outcome for ibrutinib. Treatment with ibrutinib leads to 12.2 LYs and 8.43 QALYs, while GCib leads to 10.4 LYs and 7.26 QALYs (Table 3 – “Discounted”). However, the total costs for ibrutinib treatment are much higher, since this treatment leads to €432,224 of additional costs compared to GCib. Combining the costs and effects, ibrutinib improves health at an additional cost per QALY of €369,657 and an additional cost per LY of €240,913. There is no official cost-effectiveness threshold in the Netherlands. In addition, there is no consensus on the disease burden of CLL determining the ‘soft’ threshold. But even with the highest threshold of €80,000 per QALY gained, ibrutinib is not cost-effective.

Ibrutinib leads to 1.79 more LYs than GCib but also the distribution of these LYs over the health states differs from GCib. Patients receiving GCib spend most of their time in the progression state while patients receiving ibrutinib spend most of their time in PFS. The difference in QALYs between the two treatments is however not as large as might be expected, probably since the difference in utility between PFS receiving oral treatment and progression is rather small (Table 2).

The results just mentioned are the discounted results. The conclusion on cost-effectiveness does not change when the effects and costs are not discounted. The incremental costs per QALY gained and LY gained are € 405,834 and € 269,795 respectively (Table 3 – “Undiscounted”).
Table 3. Base case results of the CUA of ibrutinib compared to GClb

<table>
<thead>
<tr>
<th>Variables</th>
<th>Discounted Ibrutinib</th>
<th>GClb</th>
<th>Difference</th>
<th>Undiscounted Ibrutinib</th>
<th>GClb</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total life years</td>
<td>12.2</td>
<td>10.4</td>
<td>1.79</td>
<td>13.8</td>
<td>11.7</td>
<td>2.09</td>
</tr>
<tr>
<td>In PFS</td>
<td>7.57</td>
<td>2.8</td>
<td>4.77</td>
<td>8.33</td>
<td>2.8</td>
<td>5.53</td>
</tr>
<tr>
<td>In PD</td>
<td>4.63</td>
<td>7.7</td>
<td>-3.07</td>
<td>5.48</td>
<td>8.93</td>
<td>-3.45</td>
</tr>
<tr>
<td>QALYs</td>
<td>8.43</td>
<td>7.26</td>
<td>1.17</td>
<td>9.52</td>
<td>8.14</td>
<td>1.39</td>
</tr>
<tr>
<td>Cost</td>
<td>€738,067</td>
<td>€305,843</td>
<td>€432,224</td>
<td>€998,786</td>
<td>€436,094</td>
<td>€562,693</td>
</tr>
<tr>
<td>Cost per LYG (Ibru vs GClb)</td>
<td>€240,913</td>
<td></td>
<td></td>
<td>€269,795</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost per QALY gained (Ibru vs GClb)</td>
<td>€369,657</td>
<td></td>
<td></td>
<td>€405,834</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Univariate sensitivity analysis

The results from the univariate sensitivity analysis can be found in Table 4. The values used for the different parameters are based on the lower and upper range of that parameter in Table 2. Table 4 shows what the effect of the one-way sensitivity analysis is on the incremental QALYs, incremental costs and the incremental costs per QALY gained. It can be seen in the third and fourth column of Table 4 that ibrutinib leads to higher costs and to more QALYs gained compared to GClb in all cases. So the variability in the different parameters does not affect the overall result. On top of that, changing the parameters unilaterally is estimated not to lead to an ICER below €250,000 per QALY gained.

The tornado diagram in Figure 11 gives a visual representation of Table 4. The tornado diagram shows how the variability of the individual parameters can affect the ICER. It ranks the parameters according to the effect they can have. Not all distributions are shown in the tornado diagram; only the distributions leading to the highest (PFS: Lognormal) and lowest (OS: Gen. Gamma) ICER. It can be seen that the variability in the utility for the progression-free state on oral treatment and the costs of ibrutinib can affect the ICER the greatest. Using the upper bound of the utility in PFS receiving oral treatment leads to an ICER of €293,649, while using the lower bound leads to an ICER of €498,753. The costs of ibrutinib can also affect the ICER significantly. Using a 20% lower price for ibrutinib than the base case corresponds with an ICER of €286,709, while a 20% higher price corresponds to an ICER of €452,605. It can also be seen from Figure 11 that the variability in the costs for IV administration, adverse events, patient and caregiver and the price of Clb have little impact on the ICER.
Table 4. Results of the univariate sensitivity analysis of ibrutinib compared to GCib (discounted)
Probabilistic sensitivity analysis

The impact of the uncertainty in the model on the results is represented in a cost-effectiveness plane (Figure 12). It shows the combinations of incremental costs and effects for 10,000 Monte Carlo simulations comparing ibrutinib with GCib. The red diamond shows the deterministic result of the ICER comparing ibrutinib with GCib.

Almost all simulations are in the north-east quadrant of the CE-plane, corresponding to positive ICERs. So this cost-effectiveness plane shows that even when the variability of the different parameters is taken into account, it is clear that ibrutinib leads to more QALYs and to higher costs compared to GCib. The 95% confidence interval (C.I.) for the incremental QALYs is 0.260-1.97 and for the incremental costs it is €207,011-582,368. More detailed results can be found in Table 5. The cloud in Figure 12 seems to show some sort of positive relationship between costs and effects. That is in contrast with the symmetrical shapes of the cost-effectiveness clouds usually seen in CEAs.

Figure 11. Tornado diagram based on Table 4
Figure 12. Cost-effectiveness plane of ibrutinib compared to GCIB (discounted)

The cost-effectiveness acceptability curve in Figure 13 shows for every ICER threshold what the probability is of each treatment to have a positive incremental NMB. So the blue line shows for every ICER threshold what the probability is that ibrutinib is cost-effective. When a threshold of €80,000 is used there is a probability of 0% that ibrutinib is cost-effective compared to GCIB. The lines cross at €367,000 per QALY gained. At an ICER threshold of €800,000 there is still a 6% probability of GCIB to be cost-effective.
Scenario analysis

As mentioned earlier, ibrutinib is placed in the so-called ‘pakketsluis’ and the unit cost still needs to be negotiated. In the scenario analysis the relationship between the unit cost of ibrutinib and cost-effectiveness was studied. For ibrutinib to be cost-effective using the threshold of €80,000 per QALY gained, the price of ibrutinib must go down from €67.61 to €20.38. This 70% price reduction would lead to an ICER of €79,939 per QALY gained, keeping all else fixed.

The price must go down to €15.49 when the €50,000 threshold is used, and to €10.60 using the €20,000 threshold.

Results part II - early CUA of stratification test

Base-case analysis

The average treatment costs per patient are €626,264 when a stratification test is used to determine the treatment strategy (Table 6). The use of this test leads to 11.9 LYs per patient and 8.38 QALYs per patient. These are discounted results. The base case results from the previous section of treating every patient with GClb or every patient with ibrutinib are also shown in Table 6.
The use of a stratification test leads to €285,847 in additional costs per QALY gained compared to treating every patient with GClb (Table 7). So the use of this hypothetical test lowers the ICER from €369,657 (treat every patient with ibrutinib) to €285,847 (Figure 14). However, this strategy is still not cost-effective compared with a threshold of €80,000 per QALY gained. This is the case even with 100% sensitivity, 100% specificity and no cost.

When comparing the test with the option of giving every eligible patient ibrutinib you see quite different results. The test will then save €111,803 per patient but it will also lead to a loss of 0.0483 QALYs per patient. This leads to a very high ICER of €2,314,555 but that can be somewhat misleading. The test has lower costs and less effect, so this ICER in fact means the test is cost-effective compared to treating all patients with ibrutinib. The ICER falls in the so called ‘south-west quadrant’ of the cost-effectiveness plane (less effective, less costly). It is argued that the same ICER threshold should be used for the north-east quadrant (more effective, more costly) as the south-east quadrant (Klok & Postma, 2004). This would mean that the money that is saved by using the test can better be spent elsewhere within the healthcare sector to obtain more QALYs.

<table>
<thead>
<tr>
<th></th>
<th>Test vs GClb</th>
<th>Test vs Ibrutinib</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incr. Costs</strong></td>
<td>€ 320,421</td>
<td>-€ 111,803</td>
</tr>
<tr>
<td><strong>Incr. LYs</strong></td>
<td>1.46</td>
<td>-0.334</td>
</tr>
<tr>
<td><strong>Incr. QALYs</strong></td>
<td>1.12</td>
<td>-0.0483</td>
</tr>
<tr>
<td><strong>ICER</strong></td>
<td>€ 285,847</td>
<td>€ 2,314,555</td>
</tr>
</tbody>
</table>

Table 7. Incremental costs and effects of a stratification test compared to GClb and to ibrutinib (discounted)
Figure 14. Visual representation of the base case result of ibrutinib compared to GClb, and of the stratification test compared to GClb

Sensitivity analysis

Figure 15 shows the cost-effectiveness plane for the stratification test compared to GClb. The red diamond shows the deterministic result. Similar as with the strategy of treating all patients with ibrutinib (Figure 12), almost all simulations are in the north-east quadrant corresponding to positive ICERS. The plane shows that even when the variability of the different parameters is taken into account, it is clear that the stratification test leads to more QALYs and to higher costs compared to GClb. The 95% confidence interval (C.I.) for the incremental QALYs is 0.254-2.00 and for the incremental costs it is €141,642-432,519. Similar as in Figure 12, the cloud in Figure 15 does not seem to be symmetrical but it seems to show some sort of positive relationship between costs and effects.
Figure 15. *Cost-effectiveness plane of the stratification test compared to GClb (discounted)*

The cost-effectiveness acceptability curve in Figure 16 shows for every ICER threshold what the probability is of each treatment to have a positive incremental NMB. So the blue line with triangles shows for every ICER threshold what the probability is that the use of the stratification test is cost-effective. When a threshold of €80,000 is used there is a probability of 0.1% that ibrutinib is cost-effective compared to GClb. The lines cross at €287,000 per QALY gained. At an ICER threshold of €800,000 there is still a 3.4% probability of GClb to be cost-effective.
Figure 16. Cost-effectiveness acceptability curve of GCImb and the stratification test

Scenario analysis

The relationship between the unit cost of ibrutinib and cost-effectiveness was already studied in part I. However, this relationship is different when a test is used to determine which patients receive ibrutinib and which patients do not. For the stratification test to be a cost-effective strategy using the threshold of €80,000 per QALY gained, the price of ibrutinib must go down from €67.61 to €26.20. This 61% price reduction would lead to an ICER of €79,973 per QALY gained, keeping all else fixed.

For the stratification test to become cost-effective, the price must go down to €20.17 when the €50,000 threshold is used, and to €14.13 using the €20,000 threshold.
Discussion and conclusions

General conclusions

Ibrutinib is not a cost-effective treatment for unfit CLL patients in the Netherlands without previous therapy. It is associated with 1.17 more QALYs and €432,224 in additional costs compared to the current standard treatment with GClb. This leads to an ICER of €369,657 per QALY gained compared to GClb. This is much more than €80,000 per QALY gained which is the implicit ICER threshold in the Netherlands. The potential role of a stratification test that predicts, which patients need treatment with ibrutinib and which patients do not necessarily need it, was studied. This test, which is an example of precision medicine, could possibly lead to a longer life expectancy for these patients at lower costs. However, even with the use of this test, treating patients with ibrutinib is not cost effective compared to the standard treatment of GClb. The use of the test leads to a health gain of 1.12 QALYs and to €320,421 in additional costs, resulting in an ICER of €285,847 per QALY gained compared to GClb. The probability of the ICER being above €80,000 per QALY gained is 99.9%. So taking the uncertainty regarding the different parameters into account it is still clear that ibrutinib in combination with the test is not cost-effective in this setting.

The high ICER of ibrutinib for all patients and of the stratification test can be explained by the combination of high costs and limited effect. The cost of the drug ibrutinib is much higher than the drug GClb and the treatment duration is much longer. Treatment with GClb lasts for a maximum of 24 weeks, while ibrutinib needs to be taken daily until progression. This means that when patients respond well to ibrutinib, their treatment can last for years. The high expenses of treating patients with ibrutinib could have been justified by a substantial amount of QALYs gained, but the incremental QALYs gained are limited. Part of the issue is the relationship between the costs and the effects of ibrutinib. They are directly connected to each other since patients who respond well to ibrutinib will continue to use it, and this will result in higher costs. This means that with an ICER threshold of €80,000 and utility of 0.71 on oral treatment, the incremental costs of ibrutinib cannot surmount €56,800 per year. Since ibrutinib treatment costs around €70,000 every year and GClb treatment is a one-time €33,000 expense, it is clear that ibrutinib cannot be cost-effective with the current price.

An additional explanation for not being cost-effective could be the high starting age of the model cohort (73). The increasing background mortality after the age of 73 forms a natural upper limit for the effect of ibrutinib. Another drawback of this relative high starting age is that the life years that are gained are not during productive years. This makes the intervention less valuable when using a societal perspective. There were practical and theoretical arguments for using 73 as the starting age. However, using a younger cohort of patients, of 60 years old for example would not
have made ibrutinib or the stratification test cost-effective. To calculate the productivity losses the friction method is used in the Netherlands (Hakkaart-van Roijen et al., 2016). A friction period of 85 calendar days is assumed and the productivity costs per hour per working woman and man are €31.60 and €37.90 respectively. Combining this with the average working week per job in the age cohort of 60-65 (29.6 hours) and the distribution of CLL over gender, an upper limit of the productivity losses can be calculated (Statistics Netherlands, 2017d).

\[
85 \text{ calendar days} / 7 \times 29.6 \text{ hours} \times (62.4\% \times \€37.9 + 37.6\% \times \€31.6) = \€12,771.
\]

The ICER of ibrutinib and the test could go down €12,771 at the most, when productivity losses are included and the starting age would have been 60 years old. So, even with the highest estimates of difference in productivity losses, ibrutinib or the stratification test would not become cost-effective.

All these conclusions are based on using a threshold of €80,000 per QALY gained. This is the highest soft threshold in the Netherlands corresponding to conditions with the highest disease burden. However, since there is no consensus yet on how to determine the disease burden, it could be argued that the disease burden of CLL is in the lower or middle category. This is associated with an ICER threshold of €20,000 and €50,000 per QALY gained respectively. But the conclusions hold that even with the highest ICER threshold, ibrutinib nor the stratification test are cost-effective.

**Comparison with other studies**

A study on the cost-effectiveness of ibrutinib in the first-line has not been published. The novelty of this current study is a strong point, but it makes it impossible to compare the result with other studies. NICE (2017a) performed a CEA on ibrutinib in the second line. It concluded that the ICER for ibrutinib fell within the range considered as cost-effective. However, the results from this study cannot be compared to the ICER of ibrutinib in the first-line since a different (and expensive) comparator was used. Next to that, a confidential discount for ibrutinib was negotiated by the NHS.

Cost-effectiveness studies for unfit CLL patients without previous treatment usually take Clb as the comparator and not GClb. A recent study of Blommestein et al. (2016) compared GClb with Clb alone and found that GClb was a cost-effective strategy. The incremental cost-effectiveness ratio was €21,823 per QALY gained using the Dutch healthcare perspective.

Ibrutinib currently shows the most promising clinical results, and in the United States it is already the recommended treatment for unfit patients (Voorhies & Stephens, 2017). However, other first-line treatments that are cheaper and less effective than ibrutinib are also available. The cost-effectiveness of other first-line treatments compared to Clb were €43,958 for rituximab + Clb, €59,316 for rituximab + bendamustine and €82,159 for ofatumumab + Clb (Soini et al., 2016).
The estimated ICER for ibrutinib of €369,657 per QALY gained is significantly higher than the ICERs for the other options. But again, these other treatments have a duration of only several months and also these drugs have lower vial costs. This might explain the large difference.

Policy implications

The price of ibrutinib has a big impact on the ICER. This high price is not justified by a large improvement in health outcome, quantified by the ICER of around €400,000 per QALY gained. This high ICER makes reimbursement of ibrutinib questionable for first-line treatment. The Dutch Minister of Health can use this study in the process of negotiating a lower price. To make ibrutinib a cost-effective treatment (<€80,000 per QALY gained) the negotiated price should be lower than €20.38 per tablet.

A straightforward price reduction is one way to increase the probability of ibrutinib being cost-effective. Another option is to negotiate a price volume agreement. In this case the price of ibrutinib will be reduced after a pre-defined volume of tablets is reached. A more complex option is to negotiate a performance-based arrangement with the pharmaceutical company behind ibrutinib. This is defined as “an agreement as one between a payer and a pharmaceutical manufacturer where the price level and/or revenue received is related to the future performance of the product in either a research or real-world environment” (Towse, Garrison, & Puig-Peiro, 2011, p. 70). These kinds of arrangements are of particular interest in the case of ibrutinib, since the current follow-up period is rather short. A possible solution is to agree on conditional flexible pricing. The Dutch Minister of Health can decide to reimburse ibrutinib once a confidential price for ibrutinib close to or below the price mentioned above is negotiated with the pharmaceutical company. The Dutch patients that will receive ibrutinib will be monitored by independent researchers in a separate trial to collect data. Every year that follows the price of ibrutinib will be revised based on the results of this trial and new interim results of the study by Burger et al. (2015). The price can either go up or down determined by the cost-effectiveness based on these outcomes. This strategy is related to the concept of value of information that was mentioned earlier. In a situation in which there is uncertainty around the effect of a treatment and at the same the reimbursement decision regarding the treatment is associated with high costs, it could also be preferred to delay the reimbursement decision. In the meantime, more information can be collected. So if there is no agreement on a price close to or under €20.38 per tablet, or the pharmaceutical company is not willing to publish follow-up data on the Burger et al. (2015) study, the decision should be to not reimburse ibrutinib for now.

The high costs of ibrutinib lead to an estimated budget impact between €1.9 and €5.5 million per year if ibrutinib is reimbursed for the specific patient population in this study (Zorginstituut
Nederland, 2017). It is up to the Dutch policy makers to decide in what way they take this budget impact into account.

**Limitations**

It should be noted that this analysis has several limitations. One of the most important is the lack of a RCT directly comparing ibrutinib and GCib. This is preferred because it gives the most reliable result when comparing a new treatment with the standard care (Hakkaart-van Roijen et al., 2016). The indirect comparison in the study leads to uncertainty regarding the ICER of a hypothetical test. As can be seen in Table 1 the characteristics of the patients in the two RCTs are comparable. However, the validity of the common comparator can be questioned. The median PFS of chlorambucil treatment is 11.1 months in the RCT on GCib (Goede et al., 2014) and 18.9 months in the RCT on ibrutinib (Burger et al., 2015).

As mentioned earlier, assumptions needed to be made on how to model the PFS and OS of patients with a complete response to GCib. The assumptions on the progression-free period and the survival curves these patients were based on the best available information from clinical trials. The use of survival curves of Clb in the first line has potentially led to an overestimation of the effect of the stratification test for reasons discussed before. But since the test in the end was estimated not to be cost-effective, these assumptions did probably not influence the conclusion.

Another important limitation is the lack of long-term data in both trials used for extrapolation. Due to the relatively short follow-up and good response to both treatments the median overall survival is not reached in the RCTs. This increases the uncertainty in the different distributions. There is no statistical solution to this inherent limitation. More data will be available in the future since updated results of the ibrutinib trial are assumed to be published in December 2017. A more reliable estimate of the cost-effectiveness can be made at that moment.

Furthermore, utility values should preferable be obtained from the population of interest, in this case the Netherlands. Due to unavailability of these data the values from the general public of the United Kingdom were used. Differences between the value sets across countries can be considerable so it is not advisable to directly transfer utilities from one country to another country without adjusting it (Knies, Evers, Candel, Severens, & Ament, 2009). The UK and the Netherlands show similar preference scores according to valuation studies, although the scores in the Netherlands are somewhat higher (Lien et al., 2015). Although the variability in the utility values does not change the conclusion on cost-effectiveness of the two interventions, better estimates of utility are needed in the future. The utility values currently used in cost-effectiveness studies do not reflect the specific side effects or the hassle of taking a certain drug. The improvement of the health related
quality of life of new CLL treatments is currently not well reflected in the utility values. This results in an underestimation of the cost-effectiveness.

In addition, a potential limitation is that the costs of adverse events of patients receiving ibrutinib that were used in the analysis could very well be an underestimation of the real costs. Now these adverse events are assumed to be a one-time event in the first cycle as is commonly done in cost-effectiveness analyses. However, ibrutinib needs to be taken until progression which can take years. If these adverse events reoccur during the treatment, the costs for ibrutinib treatment will go up. This would results in ibrutinib and the stratification both to become less cost-effective.

The use of the arbitrary range of 20% for some of the costs in the sensitivity analysis can also be seen as a limitation. It is not based on scientific evidence but merely on the approach in other CEAs studying CLL. The 20% range in the costs did not affect the conclusions regarding the cost-effectiveness of ibrutinib. In an extension to the sensitivity analysis discussed earlier it was analyzed how much these individual costs have to change in order to make ibrutinib cost effective. It turned out that even a tenfold increase in the price of GClb does not make ibrutinib cost effective. This is also true for the costs of adverse events. Supportive care costs during PFS can in no way influence the conclusions, while the supportive care costs during PD have to increase 700% in order for ibrutinib to be cost-effective. As discussed earlier, ibrutinib will become cost-effective after a 70% price reduction. So while the sensitivity range of 20% for some of the costs is rather arbitrary, a somewhat larger range would not have changed the results.

The ICER for the stratification test did not include any costs for the predictive test. As mentioned earlier predictive tests are usually genetic tests. Since the predictive test for CLL has not been developed, the price is unknown. However, looking at current tests can give an indication for the price. Complex hereditary research costs around €1,500 in the Netherlands (UMCG, 2017). A systematic review of Berm et al. (2016) found much lower costs. These so called pharmacogenetic and pharmacogenomic screening tests varied in costs between US$72 and US$575. Compared to the total costs of the two treatments (€305,843 and €738,067) these costs for a test are negligible. In addition, the analysis showed that even a free and perfect test is not cost-effective. So a good understanding of the possible costs of the test is not really needed.

Despite all these limitations it seems not very likely that the actual conclusion about the cost-effectiveness could have been affected by them.

Future research
In the indirect comparison ibrutinib seems to significantly outperform GClb, but it would be valuable to test this in a RCT. Patients can benefit from ibrutinib but this first needs to be proven in a
randomized setting. That is also the missing information in current cost-effectiveness studies on ibrutinib. New clinical trials should provide this information. Current clinical trials for front-line CLL therapy include a variety of drug combinations with ibrutinib, like venetoclax and obinutuzumab (Voorhies & Stephens, 2017). So, also in future cost-effectiveness studies regarding CLL ibrutinib will be an important drug to take into account. In addition, the quality of a future CEA can be greatly improved if the collection of economic data would be integrated in the clinical trial. This is also what the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) advises in their 2014 report (Ramsey et al., 2015). Less assumptions would be needed in the CEA which would improve the reliability of the results.

The results show that the stratification test is not close to the cost-effectiveness threshold for treatment naïve patients. A subsequent CEA could therefore focus on a predictive test for previously treated CLL patients. Treatments for relapsed patients might offer better candidates for precision medicine. These previously treated patients have a worse prognosis than patients receiving first-line therapy. This could mean that there is a bigger opportunity of improvement in life expectancy by using precision medicine. Combined with similar costs for ibrutinib, a stratification test might have a bigger probability of being cost-effective than a test in the first line.

While this study showed that a possible stratification test cannot be cost-effective, it should not discourage designers of these kinds of tests in their efforts. Patients can benefit from a possible test since the use of the test in combination with ibrutinib is estimated to lead to more QALYs. When looking at the economic side of using this test, it is the price of ibrutinib that seem to be the limitation. If ibrutinib would be a lot cheaper (<€20.38 per tablet) then it would not really be needed to develop the test. Ibrutinib would already be cost effective so all patients could receive it and thereby gain more QALYs. A situation in which the price of ibrutinib lies between €20.38 and €26.20 would favor the development of the stratification test. Keeping all else fixed, the test can in this case lead to more QALYs and make the use of ibrutinib cost effective.
References


NICE. (2017b, July 5). *Ibrutinib for untreated chronic lymphocytic leukaemia without a 17p deletion or TP53 mutation (terminated appraisal)*. Retrieved from National Institute for Health and Care Excellence: https://www.nice.org.uk/guidance/ta452/resources/ibrutinib-for-untreated-
chronic-lymphocytic-leukaemia-without-a-17p-deletion-or-tp53-mutation-terminated-appraisal-pdf-82604841741269


Appendices

Appendix A – Comparison of goodness-of-fit for different parametric distributions for the CEA of ibrutinib vs. GC\(Lb\)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>GC(Lb)</th>
<th>GC(Lb)</th>
<th>Ibrutinib</th>
<th>Ibrutinib</th>
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</thead>
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<tr>
<td></td>
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<td>OS</td>
<td>PFS</td>
<td>OS</td>
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<tr>
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<td>Gen. Gamma</td>
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<td>1508.3</td>
<td>587.9</td>
<td>188.7</td>
<td>62.0</td>
</tr>
<tr>
<td>Lognormal</td>
<td>1530.7</td>
<td>598.5</td>
<td>190.8</td>
<td>66.6</td>
</tr>
<tr>
<td>Gen. Gamma</td>
<td>1513.1</td>
<td>585.9</td>
<td>193.0</td>
<td>61.3</td>
</tr>
</tbody>
</table>
Appendix B – Kaplan-Meier curves for overall survival of Clb and G-Clb, and fitted curves for G-Clb based on hazard ratio of Clb [Goede, 2015]

![Kaplan-Meier curves for overall survival of Clb and G-Clb, and fitted curves for G-Clb based on hazard ratio of Clb](image)

Appendix C – Comparison of goodness-of-fit for parametric distributions in Appendix B

<table>
<thead>
<tr>
<th></th>
<th>Clb</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Exponential</strong></td>
<td>400.0</td>
</tr>
<tr>
<td>A</td>
<td><strong>Weibull</strong></td>
<td>400.5</td>
</tr>
<tr>
<td>I</td>
<td><strong>Log-logistic</strong></td>
<td>404.9</td>
</tr>
<tr>
<td>C</td>
<td><strong>Lognormal</strong></td>
<td>402.2</td>
</tr>
<tr>
<td></td>
<td><strong>Gen. Gamma</strong></td>
<td>401.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Clb</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Exponential</strong></td>
<td>402.8</td>
</tr>
<tr>
<td>B</td>
<td><strong>Weibull</strong></td>
<td>406.0</td>
</tr>
<tr>
<td>I</td>
<td><strong>Log-logistic</strong></td>
<td>410.4</td>
</tr>
<tr>
<td>C</td>
<td><strong>Lognormal</strong></td>
<td>407.6</td>
</tr>
<tr>
<td></td>
<td><strong>Gen. Gamma</strong></td>
<td>409.6</td>
</tr>
</tbody>
</table>
Appendix D – Treatment schedule according to HOVON (2016)

**GClb (6 cycles)**
Chlorambucil:
10mg/m² per os day 1-7, 4 weeks.

Obinutuzumab:
cycle 1 first infusion 100mg+900mg day 1,2; then 1000mg day 8 and 15; cycle 2-6 1000mg, 4 weeks

**Ibrutinib**
420mg (3 capsules) every day per os, continue till progression

Appendix E – Adverse events of grade 3, 4 or 5 with an incidence of 3% or higher

<table>
<thead>
<tr>
<th>Event</th>
<th>GClb</th>
<th>Ibrutinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>33%</td>
<td>10%</td>
</tr>
<tr>
<td>Infusion-related reactions</td>
<td>20%</td>
<td>*</td>
</tr>
<tr>
<td>Infections</td>
<td>12%</td>
<td>4%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>10%</td>
<td>*</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>4%</td>
<td>*</td>
</tr>
<tr>
<td>Anemia</td>
<td>4%</td>
<td>6%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>*</td>
<td>4%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>*</td>
<td>4%</td>
</tr>
</tbody>
</table>

* incidence lower than 3%
### Appendix F – Cost of progression state

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Monthly cost (Euros 2012)</th>
<th>% patients observed in PHAROS</th>
<th>Average monthly costs without F, FC, FCR (Euros 2017)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wait and see</td>
<td>116</td>
<td>0%</td>
<td>€ 0.00</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>508</td>
<td>34%</td>
<td>€ 184.93</td>
</tr>
<tr>
<td>Fludarabine (o/i.v.)</td>
<td>1,654</td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td>Fludarabine, cyclophosphamide (FC)</td>
<td>2,280</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>FCR (FC plus rituximab)</td>
<td>2,512</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Other rituximab combination</td>
<td>2,694</td>
<td>27%</td>
<td>€ 778.81</td>
</tr>
<tr>
<td>Rituximab monotherapy</td>
<td>3,042</td>
<td>7%</td>
<td>€ 227.99</td>
</tr>
<tr>
<td>Alemtuzumab monotherapy</td>
<td>4,205</td>
<td>1%</td>
<td>€ 45.02</td>
</tr>
<tr>
<td>Induction therapy</td>
<td>3,013</td>
<td>0%</td>
<td>€ 0.00</td>
</tr>
<tr>
<td>Conditioning therapy + AlloSCT</td>
<td>7,932</td>
<td>0%</td>
<td>€ 0.00</td>
</tr>
<tr>
<td>Transformation therapy</td>
<td>1,877</td>
<td>0%</td>
<td>€ 0.00</td>
</tr>
<tr>
<td>FCA (FC + Alemtuzumab)</td>
<td>22,131</td>
<td>0%</td>
<td>€ 0.00</td>
</tr>
<tr>
<td>Other chemotherapy</td>
<td>809</td>
<td>5%</td>
<td>€ 43.31</td>
</tr>
</tbody>
</table>

**Total average costs per month (Euros 2017)**: € 1,855.17

**Total average costs per model cycle (Euros 2017)**: € 856.23

### Appendix G – Costs for patient and caregivers

<table>
<thead>
<tr>
<th>Costs for patient and family</th>
<th>Amount</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average distance to hospital (km)</td>
<td>7</td>
<td>Hakkaart-van Roijen et al. (2015)</td>
</tr>
<tr>
<td>Price per km</td>
<td>€ 0.19</td>
<td>Hakkaart-van Roijen et al. (2015)</td>
</tr>
<tr>
<td>Parking costs per visit</td>
<td>€ 3.00</td>
<td>Hakkaart-van Roijen et al. (2015)</td>
</tr>
<tr>
<td>Taxi per km</td>
<td>€ 2.66</td>
<td>Hakkaart-van Roijen et al. (2015)</td>
</tr>
<tr>
<td>Taxi starting fare</td>
<td>€ 2.95</td>
<td>Hakkaart-van Roijen et al. (2015)</td>
</tr>
<tr>
<td>Time costs for caregivers, replacement costs per hour</td>
<td>€ 14.00</td>
<td>Hakkaart-van Roijen et al. (2015)</td>
</tr>
<tr>
<td>Percentage living alone in NL (70-75 yrs)</td>
<td>0.253228</td>
<td>CBS (2016)</td>
</tr>
<tr>
<td>Total hours away from home per GClb treatment</td>
<td>5 (a)</td>
<td>Chen et al. (2017)</td>
</tr>
<tr>
<td>Total hours away from home per monitoring visit</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Percentage of the people living alone - taken to hospital by caregiver</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Percentage of the people living together - taken to hospital by caregiver</td>
<td>50% (b)</td>
<td></td>
</tr>
<tr>
<td>Percentage of the people taken to hospital by partner - by taxi</td>
<td>50% (c)</td>
<td></td>
</tr>
</tbody>
</table>

(a) 4 hours treatment + 1 hour driving/waiting; (b) other 50% by partner; (c) other 50% by own car.
Appendix H – Kaplan-Meier and fitted curves for progression-free survival and overall survival with chlorambucil treatment
Appendix I – Comparison of goodness-of-fit for different parametric distributions of chlorambucil treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Clb PFS</th>
<th>Clb OS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exponential</td>
<td>474.5</td>
<td>292.6</td>
</tr>
<tr>
<td>Weibull</td>
<td>473.1</td>
<td>294.5</td>
</tr>
<tr>
<td>Log-logistic</td>
<td>473.1</td>
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<tr>
<td>Lognormal</td>
<td>472.9</td>
<td>296.9</td>
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<tr>
<td>Gen. Gamma</td>
<td>474.4</td>
<td>294.9</td>
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<tr>
<td><strong>B</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exponential</td>
<td>477.1</td>
<td>295.1</td>
</tr>
<tr>
<td>Weibull</td>
<td>478.3</td>
<td>299.7</td>
</tr>
<tr>
<td>Log-logistic</td>
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<td>301.9</td>
</tr>
<tr>
<td>Lognormal</td>
<td>478.1</td>
<td>302.0</td>
</tr>
<tr>
<td>Gen. Gamma</td>
<td>482.2</td>
<td>302.7</td>
</tr>
</tbody>
</table>